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**Psychiatry's next top model: Cause for a re-think on drug models of psychosis and other psychiatric disorders**

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Key words: model, pharmacology, psychosis, drugs, depression, alcohol, cannabis, psilocybin, ketamine, amphetamine

## **Abstract**

Despite the widespread application of drug modelling in psychiatric research, the relative value of multiple models has never been formally compared in the same analysis. Here we compared the ability of 5 drugs (cannabis, psilocybin, amphetamine, ketamine and alcohol) to model psychiatric symptoms in a two-part subjective analysis. In the first part, mental health professionals associated statements referring to specific experiences, e.g. ‘I don’t bother to get out of bed’, to one or more psychiatric symptom clusters e.g. depression and negative psychotic symptoms. This measured the specificity of an experience for a particular disorder. In the second part, individuals with personal experience with each of the above-listed drugs were asked *how reliably* each drug produced the experiences listed in part 1, both acutely and sub-acutely. Part 1 failed to find any experiences that were specific for negative or cognitive psychotic symptoms over depression. The best model of positive symptoms was psilocybin and the best models overall were the acute alcohol and amphetamine models of mania. These results challenge current assumptions about the relative value of drug models and motivate further research on this understudied issue.

## **Introduction**

Drug models of mental illness are useful in psychiatry as they help to inform hypotheses on the biology of pathological states and provide a valuable testing ground for novel medications. Psychosis has proved a popular domain for drug models. Psychotomimetics (psychosis-mimickers) that have received particular attention include: cannabis or delta-9-tetrahydrocannabinol (THC) (Kalant, 1971), serotonergic psychedelics such as psilocybin and LSD (Hoch et al., 1952), amphetamines (Bell et al., 2009) and the dissociative anaesthetic agents phencyclidine (PCP) and ketamine (Luby et al., 1959, Johnson, 1971). However, few studies have compared the relative accuracy of drug models in a controlled manner

(Gouzoulis-Mayfrank et al., 2005), and consequently, it is difficult to say which drug offers the most complete model of psychosis.

It has been claimed that certain drugs can reliably produce spiritual-type experiences that are indistinguishable from spontaneously occurring spiritual experiences (Griffiths et al., 2006). However, clinicians sometime identify such phenomena as psychopathological (Moreira-Almeida, 2012). Thus, this study also sought to address this matter by enquiring about: 1) the specificity of apparent spiritual experiences over psychopathological symptoms, and 2) the reliability with which such states can be induced by different drugs.

A comparison of the relative strengths and weaknesses of different drug models of mental states is fraught with difficulty. For example, the same drug may induce different effects in different people (e.g. drug naïve research volunteers versus experienced drug users) and in different social contexts (e.g. in a clinical study versus at home). Two factors are especially important when evaluating a model of a disorder: 1) How closely the features of the model resemble the symptoms of a *specific* disorder, and 2) How often these features occur in the model. In the context of drug models of psychiatric disorders, an optimal model should reliably produce an experience that is typical of a *specific* disorder. This would effectively imply that the drug-induced and endogenous states are so similar and distinctive that strong inferences can be made about the endogenous state based on the induced state.

It is a relatively simple task to determine the reliability with which a drug can produce an endogenous state. However, determining the degree to which a particular experience is uniquely or exclusively associated with a particular disorder or symptom cluster is slightly more complicated. For example, if the experience of finding it difficult to concentrate is

common to a range of disorders, then a drug that makes it difficult for someone to concentrate will not be useful in making predictions about one disorder compared with another. As will be discussed below, the issue of the degree to which a drug model is uniquely associated with a given illness has been neglected in previous model evaluations.

In this 2-part study, using novel methodologies, we sought to address an important and unanswered question: what are the best drug models of psychiatric illness? This subjective study was conceived as a pilot study to motivate and inform the design of a larger controlled study.

## **Methods**

### **Basic design:**

To address the question of the relative merits of different drug models, we devised a subjective pilot study in 2 parts. In the first part, mental health professionals were contacted and asked to complete a web-based survey in which they were presented with a number of first-person statements and asked to rate how closely they resembled particular mental states or symptom clusters, namely: positive psychotic symptoms, negative psychotic symptoms, cognitive symptoms of psychosis, thought disorder, depression, anxiety, mania, and spiritual experiences.

In the second part of the study, we devised a survey to be completed by drug users with personal experience with 5 different drugs: high potency cannabis, psilocybe magic mushrooms, ketamine, amphetamine and alcohol. Respondents were presented with a subset of the statements from part 1 and asked to say whether and how often they experienced the

referred to phenomena, when under the acute influence of a drug, and in the subacute period following its use.

This study received ethical approval from Imperial College Research Ethics Committee. The surveys for each part were built using the Bristol Online Surveys service ([www.survey.bris.ac.uk](http://www.survey.bris.ac.uk)) and can be found in the supplementary material.

## **Participants:**

### **Part 1:**

A link to the part 1 survey was emailed to psychiatrists and clinical psychologists known to us who were asked to complete the survey. We also asked them to forward it onto eligible colleagues (to be eligible, respondents simply had to be mental health professionals). Sixty three mental health professionals completed the survey. Demographic data is presented in table 1.

### **Part 2:**

Two hundred and twenty four experienced drug users completed the part 2 survey. The survey was advertised on the drug user forums: [www.bluelight.ru](http://www.bluelight.ru) and [www.drugs-forum.org](http://www.drugs-forum.org), as well as the website [www.maps.org](http://www.maps.org) which is an organisation concerned with promoting clinical research with psychedelic drugs. Two hundred and twenty four individuals responded to the survey. Each was required to have taken alcohol, high potency cannabis, amphetamine, psilocybin-containing magic mushrooms and ketamine on at least one occasion.

Demographic data is presented in table 1.

## **Survey format and procedure:**

## **Part 1:**

In the part 1 survey, respondents (mental health professionals) were presented with 58 first-person statements referring to experiences or symptoms a psychiatric patient might describe (e.g. 'I feel sad', 'my thoughts stop as if they are blocked' and 'I get worried that other people are plotting against me'; see supplementary material to view all 58 statements). Seven additional statements were included that are characteristic of spiritual-type experiences - based on the available literature on its phenomenology (Stace, 1961, James, 1902). The statements themselves were generated by a consultant psychiatrist and psychosis specialist (JMS), based on his own training and experience with patients – in discussion with RCH and DJN. Respondents were instructed to ascribe each statement to up to 8 different disorders or symptom clusters: 1) mania, 2) anxiety, 3) depression, 4) positive psychotic symptoms, 5) negative psychotic symptoms, 6) cognitive symptoms of psychosis and 7) formal thought disorder. Respondents could also select: 8) spiritual experiences and 9) none of these. More than one of the 9 options could be selected for each of the 58 statements, for example: 'I feel worried or frightened' might be ascribed to anxiety and to positive psychotic symptoms. The schedule of statements was designed to cover experiences associated with a range of psychiatric disorders – plus the spiritual experience.

Seventeen statements from part 1 were selected for inclusion in part 2 based on how exclusively they were associated with a particular symptom cluster, their clinical significance and their relevance to drug-induced states. The number of statements had to be reduced because of the length of time required to complete the part-2 survey.

We calculated a statement's degree of association with a particular mental state as the number of ascriptions to that state over the number of ascriptions to other symptom clusters. This was

then expressed as a percentage. For example, for the statement: 'I become more talkative', which was most closely associated with mania, its degree of association was calculated by summing the number of ascriptions to mania (61) over the total number of ascriptions to any mental state (96) + 61. That is,  $61/96 * 100 = 64\%$ , or 'I become more talkative' had a 64% association with mania. The 17 first person statements that were selected for the part 2 survey are shown in figure 1.

## **Part 2:**

For each statement, respondents were instructed to select (from options 'rarely/never', 'sometimes' or 'often/always'), the frequency with which they experienced the effect described by each statement after taking at least a moderate dosage of each drug.

Respondents were asked to do this for both the acute drug effects – i.e. the immediate 'high' – and separately for the post-acute effects – i.e. the comedown or withdrawal period. The following doses were provided as guidance of what was meant by a 'moderate' dose:

Cannabis: at least one well loaded spliff/joint, deeply inhaled and shared between no more than two people, or at least one 'bowl' in a bong or pipe shared by no more than two people;  
alcohol: >3 pints of medium to high strength beer or cider, or at least 3 large glasses of wine;  
psilocybe mushrooms: at least 12 fresh liberty cap magic mushrooms or at least 1g of psilocybe cubensis; amphetamine: at least 500mg snorted or bombed amphetamine;  
ketamine: over 60mg snorted.

## **Data Analysis for the part 2 survey:**

We quantified a drug's ability to induce a particular symptom cluster or mental state as the mean percentage of part 2 respondents selecting 'always/often' for statements associated with a particular symptom cluster. For example, 77% of respondents said that acute amphetamine



always or often made them more talkative, 24% said it always/often made them less worried about spending money or doing dangerous things and 34% said it always/often makes their thoughts go so quickly others can't keep up with them. Thus, acute amphetamine's 'reliability' to induce mania-related symptoms is  $(77+24+34)/3$  or 45%. The results of the part 2 survey are shown in figure 2.

## **Results**

Demographic data are presented in Tables 1.

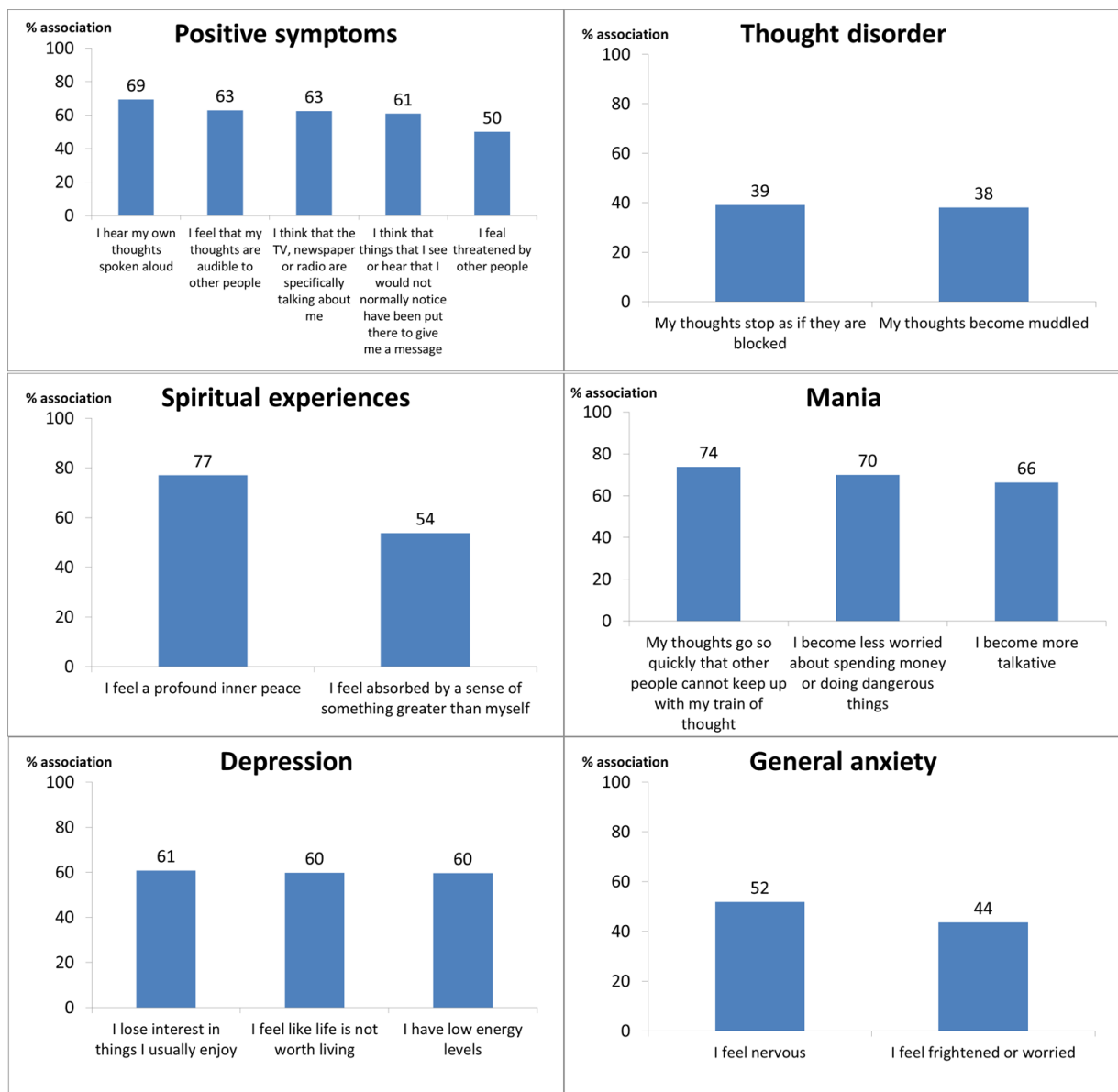
| Part 1: mental health workers |     |    |
|-------------------------------|-----|----|
| Profession                    | N   | %  |
| Psychiatrist                  | 55  | 87 |
| Psychologist                  | 8   | 13 |
| Speciality                    |     |    |
| Depression                    | 24  | 38 |
| Bipolar/mania                 | 26  | 41 |
| Psychosis                     | 30  | 48 |
| Anxiety                       | 23  | 37 |
| Addiction                     | 21  | 33 |
| Spirituality                  | 6   | 10 |
| Country                       |     |    |
| Britain                       | 48  | 76 |
| Other in Europe               | 4   | 6  |
| United States                 | 6   | 10 |
| Australia                     | 3   | 5  |
| Other                         | 2   | 3  |
| Part 2: drug users            |     |    |
| Sex                           | n   | %  |
| Male                          | 178 | 79 |
| Female                        | 46  | 21 |
| Nationality                   |     |    |
| British                       | 51  | 23 |
| Irish                         | 3   | 1  |
| Other European                | 25  | 11 |
| American                      | 113 | 50 |
| Australian                    | 12  | 5  |
| Canadian                      | 15  | 7  |
| Other                         | 5   | 2  |
| Found survey on:              |     |    |
| bluelight.ru                  | 124 | 55 |
| drugs-forum.com               | 30  | 13 |
| maps.org                      | 57  | 25 |
| Other                         | 13  | 6  |

**Table 1. Demographic data for the sample of respondents to both surveys:** A total of 63 mental health professionals completed the part 1 survey and 224 experienced drug users completed part 2 survey. In the part 1 survey, respondents could select more than one speciality. Most respondents were psychiatrists (87%) and the remainder were psychologists. Seventy six percent were British. Most of the respondents in part 2 were male (79%), 50% were American and 23% were British.

### **Part-1 results:**

Figure 1 displays each symptom cluster and the statements that had the greatest degree of association with them. None of the statements had any significant unique association with negative psychotic symptoms or cognitive symptoms of psychosis. This was mainly due to a high co-association between 4 symptom clusters: depressive symptoms, thought disorder, negative psychotic symptoms and cognitive symptoms of psychosis. For example, the statement 'I can't concentrate on things' had a unique association of only 28% for its most closely related symptom cluster, depression, because although 90% associated this statement with depression, respondents also associated it with mania (37%), anxiety (49%), thought disorder (30%), negative symptoms of psychosis (17%) and cognitive symptoms of psychosis (43%). Indeed, even if negative symptoms and cognitive symptoms were collapsed into one symptom cluster (on the basis that they all describe functional deficits), no new statements were identified that had specificity for this single symptom cluster.

The statements relevant to mania were the most uniquely or exclusively associated (70% mean association). Excluding negative and cognitive symptoms, for which no statements were uniquely associated, the symptom cluster with the least uniquely associated statements was thought disorder, with a mean association of 38.5%.



**Figure 1. Part 1 survey results:** These charts display the 17 first person statements that were used in the part 2 survey. Each chart shows the statements belonging to a particular disorder or symptom cluster and their degree of association with that symptom cluster. The title of the y axis, ‘specificity’, is synonymous with ‘exclusivity’ or the closeness of the association.

## **Part 2 results:**

### **Drug models of positive psychotic symptoms:**

The results of the part 2 survey are displayed in figure 2. The first notable result was that none of the classic drug models of psychosis produced positive psychotic symptoms with any reliability. The best model of positive symptoms was acute psilocybin; however, even this had a low reliability of just 13% (i.e. 13% of respondents reported often or always experiencing positive symptoms after psilocybin), suggesting that although it was the best drug model of positive symptoms, it is not an especially reliable model.

### **Drug models of thought-disorder:**

The best drug model of thought disorder was acute ketamine (27% reliability). However, even ketamine's association with this symptom cluster showed that it was not especially reliable. Acute and sub-acute alcohol had a relatively high association with thought-disorder at 22% and 18% respectively.

### **Drug models of the spiritual experience:**

The best drug model of the spiritual experience was sub-acute psilocybin with 37% reliability, followed by acute ketamine (33%) and psilocybin (30%). Acute and sub-acute psilocybin (53% and 48% reliability respectively) were closely associated with the statement 'I feel a profound inner peace'. In part 1, this statement was the most exclusively associated with a 'symptom cluster' or mental state, with an association of 77% for the spiritual experience (fig 1).

**Drug models of mania:**

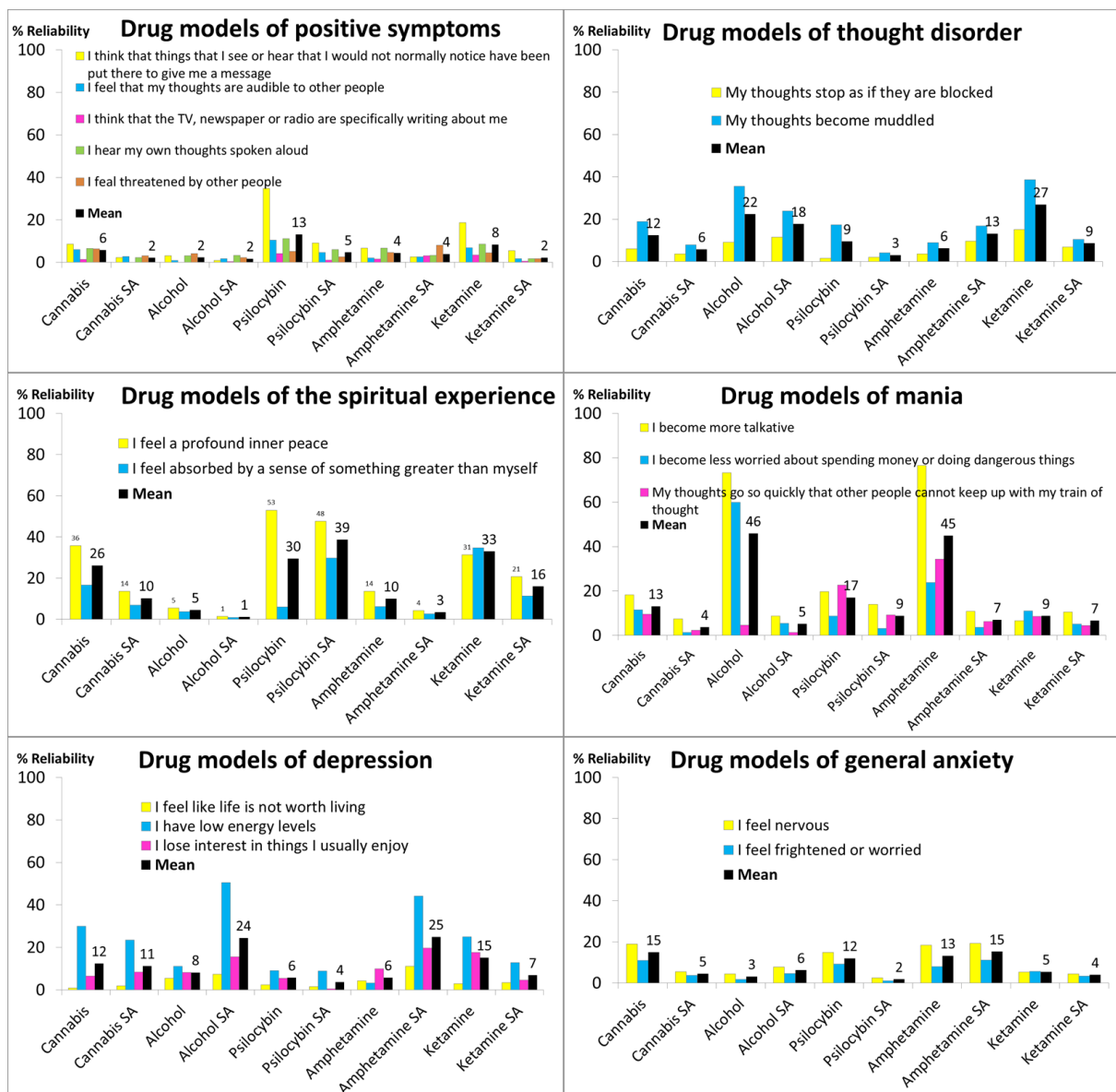
The best drug model of mania was acute alcohol (46% reliability), closely followed by acute amphetamine (45%). The reliability with which acute alcohol and ketamine could produce manic symptoms was the highest of all of the drug-symptom associations.

**Drug models of depression:**

The 2 drugs that reliably produced manic symptoms when taken acutely were also those that most reliably produced depressive symptoms sub-acutely. Sub-acute alcohol and ketamine's degree of association with depression was 24% and 25% respectively.

**Drug models of general anxiety:**

None of the 5 drugs produced symptoms of anxiety with any reliability. Acute cannabis (15%) and sub-acute amphetamine (15%) had the highest reliability to induce anxiety-related effects.



**Figure 2. Part 2 survey results:** Each chart represents a disorder or symptom cluster and the first-person statements associated with it, as determined by the results of the part 1 survey. The x-axis features the 5 different drugs enquired about in the survey, the acronym ‘SA’ is for ‘sub-acute’. The y-axis displays the percentage of respondents reporting that they ‘always or often’ have the relevant experience under the relevant drug. The black bar in each chart represents the mean of the different statements within the symptom cluster.

## Discussion

A number of interesting findings emerged from this novel analysis. Firstly, none of the 4 classic drug models of psychosis produced positive psychotic symptoms with any reliability. Psilocybin emerged as the best model of positive symptoms, which is consistent with the finding of a previous controlled study that compared the psychotomimetic properties of the psychedelic drug dimethyltryptamine with those of the dissociative ketamine (Gouzoulis-Mayfrank et al., 2005). Nevertheless, only 13% of psilocybin users claimed to always or often experience positive psychotic symptoms after this drug. Indeed, drugs were less likely to produce positive psychotic symptoms than any of the other symptom clusters. This is in contrast to studies of acute administration of these drugs in a laboratory setting, in which positive psychotic symptoms are commonly reported (Krystal et al., 1994, Gouzoulis-Mayfrank et al., 2005, Morrison et al., 2009).

There are many possible reasons for this discrepancy. One is that the survey was completed by experienced drug users who may be more resilient to psychotomimetic effects than drug-naïve healthy subjects. These individuals may be more reluctant to disclose adverse responses due to positively biased perspectives on these drugs, as well as ‘bravado’ - especially in the case of males (McLean and Anderson, 2009) who dominated the sample (80%). Furthermore, individuals who experience psychotic effects with these drugs may be less likely to take them recreationally and to frequent the websites on which this survey was advertised. It is also possible that the doses used in clinical studies have been higher, and the participants less experienced, or that clinical studies may be affected by implicit biases, especially where clinician administered scales are used. However, perhaps the most likely explanation for the discrepancy is that reactions to psychotomimetic drugs are known to be highly sensitive to the context in which they are taken. For example, the same drug, self-administered in a



comfortable setting is less likely to elicit paranoid reactions than if it is administered by an unfamiliar person in an unfamiliar setting.

A key question when evaluating a drug's ability to model a multifarious condition like psychosis is: what *specific aspect* of the disorder is the drug supposed to be modelling?

Auditory-verbal hallucinations are common in acute psychosis but very rare in drug states (Gouzoulis-Mayfrank et al., 1998), whereas anxious states engendering false inferences are much more common (Fletcher and Frith, 2009, Corlett et al., 2009, Mathys et al., 2011). This is supported by the sensitivity of psilocybin for the statement: 'I think that things that I see and hear that I would not normally notice have been put there to give me a message' (35% reported often/always experiencing this after psilocybin) which speaks to both the false inference (Fletcher and Frith, 2009) and aberrant salience (Kapur, 2003) models of psychosis. Auditory hallucinations can be thought of as *transients* in a mechanistic sense (Friston, 1997), i.e. short-lived events occurring periodically. It may be that acute drug states are incapable of modelling such phenomena. It may be more realistic to consider only how a drug can model a specific *acute state*, and transients may be merely epiphenomena of prolonged states. We might speculate that there would be a greater likelihood of auditory hallucinations if a psychotomimetic drug was taken chronically – as repeated use might kindle emergent phenomena. This hypothesis is consistent with the psychotogenic potential of cannabis (Di Forti and Murray, 2005), for which there is a high prevalence of chronic use (in contrast to psychedelic drugs, which are typically taken irregularly (Carhart-Harris and Nutt, 2010)). Fixed symptoms like auditory hallucinations may depend on a history - thus explaining why they are so difficult to model acutely.

It is often claimed that the popular ketamine model of psychosis is superior to other drug models because it models both positive and negative symptoms of psychosis (Krystal et al., 1994). However, some have questioned the construct validity of negative symptoms as they are not specific to schizophrenia (Sommers, 1985, Kaiser et al., 2011). Negative symptoms refer to such things as social withdrawal, emotional withdrawal, blunted affect and poverty of thought or speech. Statements included in the initial 58 that we thought might resonate with negative symptoms were: 'I become emotionally withdrawn', 'I lose interest in doing things', 'I don't bother to get out of bed', 'I don't want to socialise with other people' and 'I would rather not be around other people'. However, the mental health professionals who responded in the first survey were more likely to attribute these experiences to depression.

Acknowledging that cognitive symptoms of psychosis might load onto the same factor as negative symptoms, we collapsed these into a single cluster to see if an improvement in specificity could be achieved – but still no statements could be identified that were unique to this new symptom cluster over depression.

Importantly, these results do not imply that negative symptoms do not exist in schizophrenia, nor that they are seriously disabling; indeed, evidence suggest they are among the most prevalent and disabling symptoms (Ho et al., 1998). However, they do demonstrate that there is a great deal of overlap between self-reported negative and depressive symptoms and, from the present study, it is not possible to make any claims about the validity of currently proposed drug models of negative symptoms.. One possible reason why we were unable to identify any questions that were uniquely associated with negative symptoms in the present survey is that statements referring to blunted affect or to feelings of spontaneity were not included in part 1. It is possible that these statements may have been more likely to be associated with negative symptoms than depression by mental health professionals.

Perhaps the most surprising finding of the present study was the relative reliability with which acute alcohol produced symptoms of mania. Forty six percent of respondents said they often or always experienced manic symptoms after alcohol, and 45% said that they often or always experienced these after amphetamine. While amphetamine is an established drug model of mania (Mamelak, 1978), alcohol is not, and yet it produced symptoms with the highest exclusivity for any symptom cluster (70% specificity for mania). In comparing the alcohol versus amphetamine models of psychosis, it is interesting to note that alcohol was more associated with loss of inhibition about doing dangerous things, whereas amphetamine was associated with racing thoughts. It was also interesting that the best drug models of depression were sub-acute alcohol and amphetamine, with 24% of respondents reporting that they often or always experienced depressive symptoms during the alcohol hangover and 25% of respondents saying they experienced this during amphetamine withdrawal. Depression during amphetamine withdrawal has been documented before (Mamelak, 1978, Leith and Barrett, 1976, Seltzer and Tonge, 1975) as has depression post alcohol use (Sumnall et al., 2004) and acute and sub-acute amphetamine has been proposed as a model of bipolar disorder (Mamelak, 1978) but to our knowledge, the same has not been said of alcohol. Exaggerated mania has been described in manic patients presenting with concurrent alcohol misuse (Salloum et al., 2002) and so the relationship between alcohol use and bipolar disorder is worth investigating.

A particularly novel feature of the present survey was its inclusion of first person statements relevant to the spiritual experience (Stace, 1961, Hood et al., 2009). This area is receiving growing interest after it was found that profound spiritual-type experiences could be reliably elicited in healthy volunteers after a single high dose of psilocybin (Griffiths et al., 2006).

Moreover, these experiences tended to have a lasting impact, improving emotional wellbeing and increasing trait 'openness' over 12 months after the acute experience. These findings are consistent with the results of the present study since the best model of the spiritual experience was sub-acute psilocybin, with 39% of respondents saying that they often or always have spiritual-type experiences in the period following psilocybin use. Interestingly, the statement with the strongest association for any 'symptom cluster' was 'I felt a profound inner peace' (77% association with the spiritual experience). Over half of the respondents (53%) said they always or often experience this in the acute psilocybin state and 48% said they experience it in the sub-acute period following psilocybin. The unique association of statements for the spiritual experience over psychotic symptom clusters is telling as it suggests that the spiritual experience is non-pathological and distinct from psychosis (Moreira-Almeida, 2012).

This study has some important limitations. Data was derived via web-based survey and although this is an efficient means of data collection that can open up unique possibilities, it is also requires the surrender of many experimental controls. We have no control over who completes the survey and no indication about the accuracy of their replies. Moreover, the respondents may have held biases, and this is a problem with subjective assessments in general. Also, respondents gave their assessments based on recreational use in naturalistic settings whereas controlled studies administer drugs in a very different context. That context can have such a marked influence on subjective responses to a drug is important; it implies that we should be cautious about making general inferences about a drug's pharmacology based on a set of subjective reports – as a very different experiences may be produced by the same drug in a different context. Future research might try to assess drug by environment interactions in a controlled manner to better understand this phenomenon.

Another possible criticism is that we could have collected more data. For example, we could have enquired about respondents' ages and, in the case of part 2, the frequency of their drug use. However, the advantages of extending the surveys had to be balanced against the disadvantages of losing participants due to boredom or irritation with the length of the survey.

In summary, the results of the present study suggest that the best drug models of psychiatric disorders are the acute alcohol and amphetamine models of mania, since these reliably produce symptoms that are relatively exclusive to a specific disorder. The results also suggest that drug models of positive psychotic symptoms are comparatively poor, at least when the drugs are taken naturalistically by experienced users. Psilocybin emerged as the best model of positive symptoms but models of negative symptoms could not be assessed because we failed to find any experiences that were specific for this symptom cluster over depression. Lastly, sub-acute psilocybin appeared to be a reliable model of non-pathological spiritual-type experiences – which may have implications for therapeutic applications of this drug (Griffiths et al., 2008, Grob et al., 2011).

It is hoped that this pilot study will motivate a larger controlled study involving administration of a range of psychotomimetic drugs to healthy individuals. For example, in a within-subjects design, with sufficient time separating administrations, it would be interesting to compare the relative psychotomimetic properties of different drugs at different doses. It would also be interesting to incorporate rating scales for other disorders and symptom clusters (e.g. depression and specifically *early* psychotic symptoms) so that a drug's psychotomimetic properties can be more accurately and specifically defined.

To finish, it is hoped the present study has stimulated new thoughts about an understudied debate. Some of its implications challenge contemporary assumptions and therefore require follow-up by controlled research.

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